

The impact of tidal volume on pulmonary complications following minimally invasive esophagectomy: A randomized and controlled study

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Background: Minimally invasive esophagectomy (MIE) has been advantageous for lowering pulmonary complications compared with open approaches.¹ However, pulmonary complications remain the most common morbidity after surgical resection of esophageal cancer.^{2,3} The aim of this prospective, randomized, controlled, clinical trial was designed to see whether low tidal volume (VT) could further minimize pulmonary complications after MIE.

Methods: Between June 2011 and July 2012, a total of 101 patients who underwent MIE received left-lung ventilation during thoroscopic esophagectomy. All patients received left-lung ventilation during thoroscopic esophagectomy. Patients were randomly assigned to a low VT (5 mL/kg + 5 cm H₂O positive end-expiratory pressure) preserved ventilation (PV) group (n = 53) and a conventional VT (8 mL/kg) controlled ventilation (CV) group (n = 48) in the thoracic stage. Alveolar lavage fluid was harvested from the ventilated lung at intubation and at 18 hours after surgery for analysis of interleukin (IL)-1 β , IL-6, and IL-8 levels. Clinical characteristics, including patient demographics, operation features, and changes in oxygenation index, were recorded and analyzed. Pulmonary complications were identified and statistically compared between the 2 groups.

Results: The clinical characteristics and operation features were comparable between the 2 groups. IL-1 β , IL-6, and IL-8 expressions in preoperative alveolar lavage fluid were similar between the 2 groups. Significantly lower IL expressions were observed in the PV group than those in the CV group at 18 hours after MIE (IL-1 β , 25.42 \pm 31.01 vs 94.96 \pm 118.24 pg/mL; IL-6, 30.86 \pm 75.78 vs 92.99 \pm 72.90 pg/mL; IL-8, 258.75 \pm 188.24 vs 403.95 \pm 151.44 pg/mL; all $P < .05$). The 18-hour postoperative oxygenation index was lower in the CV group than that in the PV group (292.85 \pm 28.74 vs 326.35 \pm 34.43; $P = .046$). Pulmonary complications were observed in 18 cases of our series, occurring more frequently on the ventilation side (right, 6 cases; and left, 12 cases). All patients were cured by conservative therapy without severe sequelae. The occurrence of pulmonary complications in the PV group was lower than that in the CV group (9.43% vs 27.08%; $P = .021$).

Conclusions: Lung injury due to intraoperative single-lung ventilation may contribute to pulmonary complications after MIE. Low VT ventilation could decrease ventilation-associated lung inflammation, thus minimizing pulmonary complications after MIE. Further studies, based on a larger volume of populations, are required to confirm these findings. (*J Thorac Cardiovasc Surg* 2013;146:1267-74)

Pulmonary complications (PCs) are common after esophagectomy.¹⁻⁴ Recently, promising results from minimally invasive esophagectomy (MIE) were shown to lower this common morbidity after surgical resection of esophageal

cancer.^{5,6} However, the frequency of PCs remained high despite advances in minimally invasive techniques, which would lead to the study on decreasing PCs beside improvements on surgical techniques.

In a recent article from Sihag and colleagues,⁷ the authors noticed that the left lung was usually more vulnerable to PCs after MIE, suggesting that single-lung ventilation (SLV) may contribute to the PCs after thoroscopic esophagectomy. Nevertheless, little is known about SLV and its impact on PCs after MIE.

In this prospective, randomized, and controlled trial, we decreased tidal volume (VT) during thoroscopic esophagectomy to determine if this ventilation strategy could minimize PCs. Based on our 6 years of experience with MIE, we reported our primary results from a single center.

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Abbreviations and Acronyms

CV	= controlled ventilation
EtCO ₂	= end-tidal carbon dioxide concentration
ICS	= intercostal space
IL	= interleukin
MIE	= minimally invasive esophagectomy
OI	= oxygenation index
PC	= pulmonary complication
PEEP	= positive end-expiratory pressure
PV	= preserved ventilation
SLV	= single-lung ventilation
VT	= tidal volume

PATIENTS AND METHODS**Enrollment**

Written informed consent was obtained from all enrolled patients by the surgeon (L.T.) at least 1 day before the operation, after careful explanation of the procedures and goals of the study. This prospective, randomized, controlled trial was registered with ClinicalTrials.gov (NCT01194895) and was approved by the Ethics Committee of Zhongshan Hospital of Fudan University, Shanghai, China (No. 2009156).

All patients with esophageal cancer, who were eligible for 3-stage MIE at our institution between June 2011 and July 2012, were enrolled in this trial. Patient demographics and tumor characteristics were collected, and all patients received a detailed consultation after admission. Tumor lesions were clinically staged by endoscopy, tissue biopsy, thoracoabdominal computed tomography, and endoscopic ultrasonography. According to clinical assessment, the MIE inclusion criteria were as follows: (1) patients with clinically staged T1-3 N0 M0 tumors, (2) patients with no previous history of cancer, (3) patients with no previous history of neck or chest surgery, and (4) patients with an American Society of Anesthesiologists score of I to II.

The exclusion criteria for MIE were as follows: (1) patients with preexisting chronic obstructive pulmonary disease/asthma/interstitial lung disease, (2) patients with heart/liver or renal dysfunction, and (3) those receiving preoperative corticosteroid treatment.

In addition, patients were excluded from the study for the following reasons: (1) tumor invasive to the peripheral structures, (2) incidental injury requiring changes in operation, and (3) refusal to have bronchoscopy follow-up during the study.

Randomization

Randomization was performed using a computer-generated list. Patients were randomly assigned to either a low VT preserved ventilation (PV) group ($n = 53$) or a conventional VT controlled ventilation (CV) group ($n = 48$) by using sequentially numbered sealed envelopes containing information that disclosed the type of treatment to be applied.

Perioperative Management

All patients received a combination of epidural and general anesthesia, and were provided with patient-controlled analgesia postoperatively. After intravenous induction, each patient was intubated with a left-sided double-lumen endotracheal tube to accomplish deflation of the right lung during the thoracic stage. The tidal volume for SLV was set at 5 mL/kg in the PV group and 8 mL/kg in the CV group. An additional 5 cm of H₂O positive end-expiratory pressure (PEEP) was given only to the PV group during the thoracic stage. Patients were converted to double-lung ventilation (VT, 8 mL/kg) during the abdominal and cervical procedures. During the operation, patients' vital signs, including heart rate, respiratory rate, arterial blood pressure, oxygen saturation, and end-tidal carbon

dioxide concentration (EtCO₂), were followed every 5 minutes throughout the operation. The minimal oxygen saturation and maximal EtCO₂ were recorded during SLV. The initial inspired oxygen fraction was 0.5 using an oxygen-and-air mixture and was increased, if necessary, to keep a transcutaneous saturation greater than 90%. A warming blanket system and fluid warmers were used to prevent hypothermia during surgery. Standardized fluid replacement consisted of 10 mL/kg ideal body weight lactated Ringer solution (B. Braun, Melsungen, Germany) preoperatively, followed by 10 mL/kg per hour perioperatively. If mean arterial pressure was lower than 70 mm Hg for more than 5 minutes, an additional fluid challenge was achieved with 10 mL/kg hydroxyethyl starch (Voluven; Fresenius Kabi, Bad Homburg, Germany), eventually repeated once. The volumes of intravenous infusion were given according to patient's weight. All patients were extubated at the end of surgery and transferred to the intensive care unit.

Fiberoptic bronchoscopy was performed at intubation and 18 hours after surgery. Alveolar lavage samples were harvested from the ventilation side through mini-bronchoalveolar lavage under bronchoscopy.⁸ Fresh lavage samples were kept in a low-temperature (-80°C) freezer. The expression of interleukin (IL)-1 β , IL-6, and IL-8 in the lavage samples was analyzed by enzyme-linked immunosorbent assay (DY201, DY206, and DY208; R&D Systems, Inc, Minneapolis, Minn).

Surgery

All operations were performed by the same senior surgeon (L.T.) during the same period. MIE consisted of 3 stages (thoracic, abdominal, and cervical), as described previously.^{9,10} The thoracic stage included esophageal mobilization and mediastinal lymphadenectomy: Patients were placed in a semiprone position with the right arm raised above the head and the right side of the operating table slightly raised. The surgeon stood on the dorsal side of the patient, and a high-definition video monitor was set up at the opposite end. An observation port was placed at the seventh intercostal space (ICS) along the midaxillary line, and another 10-mm port was placed at the ninth ICS in the midscapular line. Two 5-mm ports were placed at the third ICS along the midaxillary line and just inferior to the tip of the scapula, respectively. An artificial CO₂ pneumothorax was achieved at a pressure of 8 mm Hg. After thoracoscopic exploration, the azygous vein was double ligated by Hem-o-locks (Weck Surgical, Teleflex, Limerick) and then divided, followed by mobilization of the thoracic esophagus, which proceeded from the tumor inspection site to the thoracic inlet cranially and to the hiatus caudally. Mediastinal lymphadenectomy was performed along bilateral recurrent laryngeal nerves and subcranial and paraesophageal stations, and the procedure was completed by placement of an intercostal drain and closure of the thoracic ports. The abdominal and cervical stages were the same as described previously.^{9,10} Jejunostomy was performed on all patients to provide enteral nutrition from the second postoperative day. The operation concluded with closure of the cervical and abdominal incisions in layers.

Pulmonary Complications

Both chest X-ray and ultrasonographic films were obtained daily to evaluate for possible PCs after surgery. According to the database by the Society of Thoracic Surgeons, PC was identified as the primary morbidity in the following cases: (1) therapeutic bronchoscopy/tracheotomy due to bronchial secretion, (2) pneumonia per clinical and radiographic criteria, (3) acute lung injury/acute respiratory distress syndrome requiring reintubation, (4) pleural effusion requiring chest drainage, and (5) pulmonary embolism.

Statistical Analysis

Clinical data for all patients were collected from the clinical database of our institution by trained surgical coordinators (W.W., H.W.). All data collected were tabulated using Microsoft Excel (Microsoft, Redmond, Wash) for further analysis. Statistical analysis was undertaken using SPSS software, version 17.0 (SPSS, Inc, Chicago, Ill). Variables were

compared using the Mann-Whitney test, the Student *t* test, and the χ^2 test. A 2-sided $P < .05$ was considered statistically significant.

RESULTS

Patient Demographics

Recruitment occurred from June 2011 through the end of July 2012. A total of 110 consecutive patients were deemed eligible for MIE at the Zhongshan Hospital of Fudan University. Four patients refused to participate in the research, and 5 patients were excluded because of tumor invasion or changes in operative technique. After enrollment and randomization, there were 53 patients allocated to the PV group and 48 patients allocated to the CV group. The flow diagram is shown in Figure 1.

According to the Union for International Cancer Control esophageal cancer TNM staging system (7th edition, 2010), there were 12 cases of pT1 (11.88%), 20 cases of pT2 (19.80%), and 69 cases of pT3 (68.32%) in the study. Two groups were comparable for clinical features and tumor characteristics (Table 1).

Operative Features

The operation and SLV durations were similar between the PV and CV groups. There was no significant difference found in the length of hospital stay, blood loss, or blood transfusion between the 2 groups. The operative features are listed in Table 2. The serum C-reactive protein concentration was close between the 2 groups (5.61 ± 0.34 vs 6.25 ± 0.22 ; $P = .743$). Patients' oxygenation was close at the intubation and at 48 and 72 hours after MIE, whereas a significantly lower oxygenation index (OI) was recorded

in CV than in PV at 18 hours after the operation (292.85 ± 28.74 vs 326.35 ± 34.43 ; $P = .046$) (Figure 2).

Alveolar Lavage and Cytokine Expression

There was no significant difference between groups regarding IL-1 β , IL-6, or IL-8 levels in the alveolar lavage fluid harvested after intubation. The IL levels were, however, significantly lower in the PV group 18 hours after MIE compared with the CV group levels (IL-1 β , 25.42 ± 31.01 vs 94.96 ± 118.24 pg/mL; IL-6, 30.86 ± 75.78 vs 92.99 ± 72.90 pg/mL; IL-8, 258.75 ± 188.24 vs 403.95 ± 151.44 pg/mL; all $P < .05$) (Figure 3).

Mortality and Morbidity

No intraoperative patient deaths occurred in either group. Reoperation was performed on one patient from the PV group because of major bleeding from incidental injury to spleen. An emergency abdominal exploration was given on the second day postoperatively. The bleeding was controlled during the operation, with the spleen preserved. Complications were observed in a total of 42 patients in our study (37.74% in PV vs 45.83% in CV; $P = .409$). A total of 18 cases of PCs were observed in this cohort (right side, 6 cases; and left side, 12 cases). Reintubation for ARDS/ALI was given in 9 patients (2 in the PV group and 7 in the CV group), who were cured by the following ventilation support for 3 to 7 days. There were 2 patients who underwent bronchoscopic suction due to pulmonary atelectasis; the secretions were cleared without severe sequelae. A chest tube was inserted into 4 patients (1 in the PV group and 3 in the CV group) for pleural

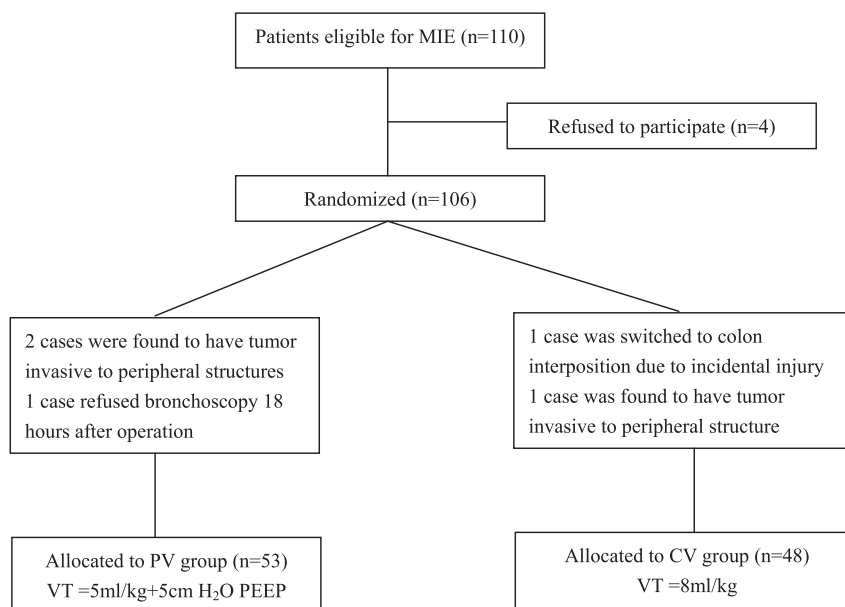


FIGURE 1. Flow diagram of the study. MIE, Minimally invasive esophagectomy; CV, controlled ventilation; VT, tidal volume; PV, preserved ventilation; PEEP, positive end-expiratory pressure.

TABLE 1. Patient demographics

Variable	PV (n = 53)	CV (n = 48)	P value
Age, y	60.5 ± 7.3	57.2 ± 9.1	.403*
Male/female ratio	40:13	32:16	.329†
Location (U:M:L)	7:38:8	10:31:7	.588†
Histologic type (SC:AD)	50:3	46:2	.909‡
Stage (T ₁ :T ₂ :T ₃)	7:11:35	5:9:34	.860‡
FEV ₁ /predicted FEV ₁ , %	92.8 ± 14.6	87.1 ± 16.9	.272*
FVC/predicted FVC, %	92.9 ± 16.2	92.5 ± 17.7	.938*
ASA (I:II)	20:33	25:23	.147†

Data are given as mean ± SD unless otherwise indicated. U, Upper; M, middle; L, lower; SC, squamous cancer; AD, adenocarcinoma; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ASA, American Society of Anesthesiologists; PV, preserved ventilation; CV, controlled ventilation. *By Student *t* test. †By χ^2 test. ‡By Fisher exact test.

effusion drainage at the contralateral side 3 to 5 days after the surgery. Pneumonia was recorded in 3 patients (1 in the PV group and 2 in the CV group) in this cohort. Intravenous antibiotics were adjusted according to the germ culture results, and all of the 3 cases recovered after conservative therapy. The occurrence of pulmonary complications in the PV group was lower than that in the CV group (9.43% vs 27.08%; $P = .021$). There was no significant difference in 30-day mortality between the 2 groups. The details regarding mortality and morbidity are shown in Table 3.

DISCUSSION

This prospective, randomized, controlled trial found a lower incidence of PCs when a low VT plus PEEP was administered during thoroscopic esophagectomy. The patients allocated to either the PV or CV group were physically stable throughout the MIE procedure. However, the oxygenation index was better and postoperative inflammatory response was lower in the PV group compared with the CV group, suggesting that low VT during SLV may prove protective and, thus, minimize PCs.

Recently, growing evidence collected from MIE has shown improved perioperative outcomes.¹¹ The most

significant benefit concerns the decrease in PCs after this procedure. In a report from Biere and colleagues,¹² MIE led to a significantly lower incidence of PCs compared with open chest esophagectomy (9% vs 29%). In another publication by Sihag and colleagues,⁷ the PC rate decreased from 43.4% to 2.6% when MIE was applied. However, the occurrence of PCs remains high in clinical practice, despite such technical advancements in surgery.

To lower the occurrence of PCs, low VT plus PEEP was first introduced for the treatment of ALI/ARDS. When compared with conventional tidal volumes, this protective ventilation strategy proved beneficial for injured lungs undergoing ventilation support.¹³ Later, a decreased inflammatory response was observed in healthy lungs after low VT ventilation.¹⁴ These promising results may lead to further application of the new technique to SLV in major operations.

Low VT during SLV was applied to other types of surgery and showed promising outcomes regarding lowering PCs.^{15,16} However, whether this ventilation strategy could also work effectively in surgery for esophageal cancer remained uncertain. In a randomized, controlled study, Michelet and colleagues¹⁷ applied low VT (5 mL/kg) plus PEEP (5 cm H₂O) to Ivor-Lewis esophagectomy and reported a lower postoperative systemic inflammatory response. However, they did not explore the incidence of PCs in detail.¹⁷

We applied a similar technique to patients who underwent MIE. We found that the ventilation outcomes were consistent with the finding of Sihag and colleagues⁷ that more PCs occurred in the left lung. These findings suggested that ventilation, as one of the invasive factors in esophagectomy, could lead to PCs after MIE.

In an effort to make MIE less invasive, this study attempted to determine if lower tidal volume plus PEEP could lower the incidence of PCs after MIE. Three-stage MIE was performed on 101 consecutive patients in our series by the same senior surgeon (L.T.) who performed more than 100 MIEs annually to minimize the technical bias caused by surgical procedure or learning curves.¹⁸ PC was defined as primary morbidity after the operation because secondary PC was more associated with aspiration or gastric leakage after the operation.¹⁹

Berry and colleagues²⁰ reported that the occurrence of aspiration was as high as 12% in patients undergoing esophagectomy. Because lymphadenectomy along the bilateral recurrent laryngeal nerves is conventionally performed during MIE, patients in this cohort were at high risk of vocal cord palsy²¹ and pneumonia due to aspiration, especially when the gastric tube was removed at 5 to 6 days after surgery.²²

In our study, another factor contributing to the exclusion of secondary PCs was the relatively high incidence of leakage (11.88%), which might lead to severe infection in

TABLE 2. Operative features

Feature	PV group (n = 53)	CV group (n = 48)	P value
Operation duration, min	214.3 ± 70.2	195.8 ± 90.5	.338*
Thoracic stage duration, min	72.2 ± 23.6	75.0 ± 18.8	.515*
Blood loss, mL	130 ± 70	140 ± 67	.728†
Blood transfusion	0	0	NA
EtCO ₂ , mm Hg	46.6 ± 5.9	39.1 ± 6.6	.001*
SPO ₂ , %	97.4 ± 2.2	96.1 ± 2.6	.902*
Crystalloid infusion, mL/kg	27.77 ± 6.94	23.95 ± 10.18	.768*
Colloid infusion, mL/kg	11.79 ± 3.96	12.19 ± 4.77	.776*
Length of stay, d	9.4 ± 3.6	10.9 ± 4.7	.651*

Data are given as mean ± SD. PV, Preserved ventilation; CV, controlled ventilation; NA, not applicable; EtCO₂, end-tidal carbon dioxide concentration; SPO₂, oxygen saturation. *By Student *t* test. †By Mann-Whitney test.

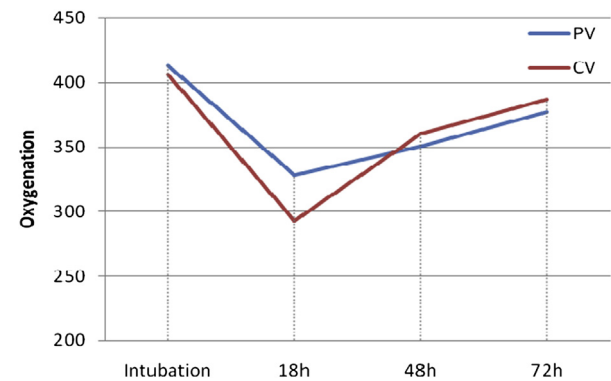


FIGURE 2. Changes in cytokines from the ventilated lung. The interleukin (IL) changes from the ventilation lung reached a significant difference between the preserved ventilation (PV) and controlled ventilation (CV) groups. (Recorded at intubation and at 18 hours after minimally invasive esophagectomy.)

the thoracic cavity and was usually observed 5 to 7 days after MIE. Luckily, the leakage did not cause higher mortality despite the high incidence, and the 2 groups were comparable regarding leakage ratio. Because there is little evidence from previous studies that MIE could decrease the leakage ratio,²³ our results suggest that further studies regarding this issue are warranted.

Despite the relatively short duration of the thoracic stage, there was a significant difference in the occurrence of PCs between high and low VT in our study, indicating that SLV may be a sensitive factor contributing to PCs after MIE. In previous publications, SLV was believed to promote ventilation-induced lung injury, resulting in a series of postoperative PCs.²⁴ Because conventional VT (8 mL/kg) was applied for double-lung ventilation, it might not be suitable for single-lung ventilation and may lead to overdistension of the remaining aerated lung and increase the shear forces generated during repetitive opening and collapse of atelectatic areas.^{25,26} Therefore, we decreased the tidal volume from 8 to 5 mL/kg during SLV. Although a higher EtCO₂ were observed in the PV group during the

TABLE 3. Mortality and morbidity

Variable	PV group (n = 53)	CV group (n = 48)	P value
Mortality	0	0	NA
Morbidity	20	22	.409*
Gastric conduit failure†	7	5	.952‡
Pulmonary complications	5	13	.021‡
Hoarseness§	4	3	.891‡
Bleeding	1	0	.960‡
Delayed gastric emptying	2	1	.931‡
Wound infection	1	0	0.960‡

PV, Preserved ventilation; CV, controlled ventilation; NA, not applicable. *By χ^2 test. †Including anastomotic leakage and gastric conduit leakage. ‡By Fisher exact test. §Including temporary and permanent palsy. ||Bleeding requiring reoperation.

thoracic procedure, the ventilation was achieved at the expense of increasing the respiratory frequency. However, postoperative hypercapnia did not result in severe perioperative outcomes. In accordance with previous publications,²⁷ we also believed that temporary hypercapnia was permissible, and the safety of the operation was not compromised in our study.

During thoracoscopic esophagectomy, the induction of pneumothorax caused collapse of the right lung to improve the exposure of the posterior mediastinum.²⁸ The left lung was kept inferior to the mediastinum within a confined space because the patient was in the semiprone position. Therefore, the ventilation-perfusion ratio of the left lung was significantly changed during the thoracoscopic procedure. In our study, the patients allocated to either the PV or CV group were stable throughout the thoracic stage, indicating that decreased VT would not lead to cardiopulmonary instability under altered V/Q correlation. Meanwhile, better postoperative OI was observed when lower tidal volume plus PEEP was given, which could be partly explained by the application of PEEP during the thoracic stage. Richard and colleagues,²⁹ who used positron emission tomography to explore the V/Q correlation in an animal model, found that PEEP and the prone position worked synergistically in improving oxygenation during

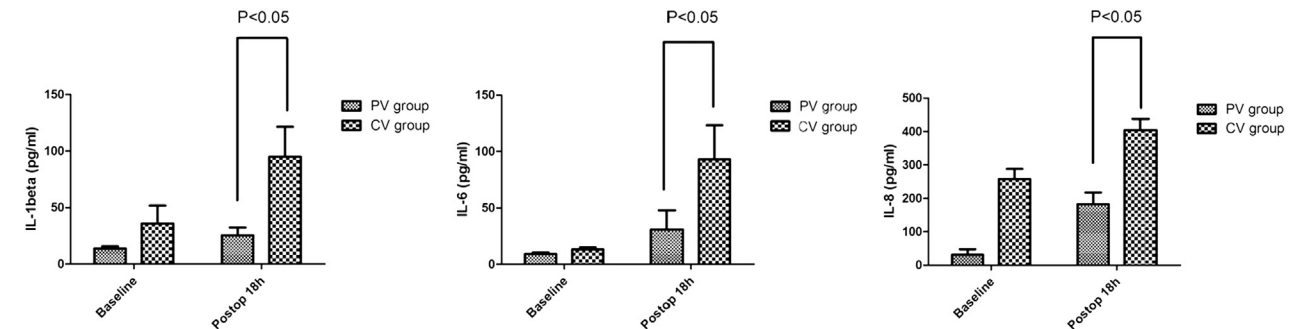


FIGURE 3. Changes in oxygenation after the operation. The oxygenation was recorded at intubation and at 18, 48, and 72 hours (h) after the operation. The 18-h postoperative oxygenation index (OI) was lower in the controlled ventilation (CV) group than that in the preserved ventilation (PV) group (292.85 ± 28.74 vs 326.35 ± 34.43; $P = .046$), whereas the OIs at other time points were close between the PV and CV groups.

ventilation. In this study, the improvements on OI were not observed in the PV group at 48 and 72 hours postoperatively because the SLV was short in duration and the effect might not last long. However, the result suggested that low VT plus PEEP is not only safe but beneficial to patients undergoing thoracoscopic esophagectomy.

Makino and colleagues²⁴ have reported remarkable changes in inflammatory response in patients undergoing esophagectomy. However, their results were based on peripheral blood samples, which is an indirect method of demonstrating the inflammatory response from a single lung.

In this study, we provided further proof of the association between ventilation and lung injury. Our laboratory findings were based on alveolar lavage collected from the left lung and, therefore, the changes in IL levels were more accurate in demonstrating the inflammatory response caused by SLV. In addition, the cytokines were recorded at intubation and 18 hours after operation, minimizing the effect of anesthesiology. Although the concentration of serum C-reactive protein was comparable between CV and PV, our laboratory findings from 3 ILs suggest a reduced regional inflammatory response due to low VT ventilation after SLV.

Because esophagectomy is a major surgical procedure associated with several traumatic manipulations, the changes in cytokine levels would normally be attributed primarily to the operation, leaving the contribution from ventilation, itself, largely obscured. We showed that ventilation is one of multiple factors contributing to PCs after MIE. The inflammatory markers used in our study were, thus, invaluable in demonstrating that the release of inflammatory mediators would lead to increased lung inflammation and possible injury to other organs.³⁰ As observed in our study, changes in bronchial cytokines may, therefore, serve as supportive evidence for the use of low VT ventilation in thoracoscopic esophagectomy.

Our study had several limitations. Because of our limited number of cases, we only performed statistical analysis on the PCs between PV and CV groups and did not compare subgroups. Future clinical studies with larger samples are needed to confirm our findings.

CONCLUSIONS

Low VT plus PEEP could decrease inflammatory response caused by SLV without affecting cardiovascular stability. It may prove to be a safe and effective ventilation strategy in minimizing PCs after MIE.

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Discussion

Dr Andrew Chang (*Ann Arbor, Mich*). Dr Shen, I congratulate you and your colleagues on a nice study.

When you talk about decreasing tidal volumes from 8 to 5 mL/kg, was that also accounting for the change from double-lung to single-lung ventilation as well? You showed that end-tidal CO₂ increased when you had gone from double lung to single lung. Did you notice any change in the peak inspiratory pressure when you were on single-lung ventilation for the 2 different tidal volumes?

Dr Shen. We changed the tidal volumes according to the previous publications. Previously, it is 8. Now, it is 5 in the single-lumen ventilation.

Dr Chang. For example, if there is a 70-kg patient, at 8 mL/kg, you would have 560 mL for a double-lung ventilation. But when you go to a single-lung ventilation and you go from 8 to 5 mL/kg, does that merely account for a single-lung ventilation?

Dr Shen. Yeah.

Dr Chang. So, then, did you look at changes in peak inspiratory pressure between double lung and single lung?

Dr Joyce. When you changed from 8 to 5 mL/kg, did you measure or did you find a difference in the inspiratory pressure?

Dr Shen. Yes. Yes. We found an elevated carbon dioxide level during the thoracoscopic esophagectomy.

Dr Chang. My next question pertained to the impact of ventilation strategy on leak rates. Typically, if someone has a pulmonary complication, we would expect them to have higher leak rates. Did you observe that in your group of patients who had more pulmonary complications? Did they have a higher leak rate at the anastomosis?

Dr Joyce. Was there a difference in the anastomotic leak rate between the groups?

Dr Shen. Can you repeat? I cannot catch it clear.

Dr Joyce. That's your question, right?

Dr Chang. Yes, it is.

Dr Joyce. Was there any difference in the anastomotic leak rate between the 2 groups?

Dr Shen. Oh, I see. You mentioned anastomotic leakage, which was interesting, and was what we cared about. The differences in anastomotic leakage were close between the 2 groups.

Dr Chang. And one final question. Thank you. Why go back to 8 mL/kg when you go to the abdominal operation portion? If you are going to do a controlled study looking at the effects of high or standard ventilation versus low-volume ventilation, why not stay at 5 mL/kg throughout the operation?

Dr Shen. We think the double-lumen ventilation will provide better results postoperatively than the single-lumen ventilation, so we changed our ventilation strategy during the abdominal and cervical stage.

Dr Chang. Okay. Thank you.

Dr Jonathan D'Cunha (*Pittsburgh, Pa*). It is a nice study, timely in the face of all the MIE experience going on around the world.

I have 3 questions. The first one, and maybe I missed it in your slide set, but did you look at the comparison between the groups in terms of their preoperative comorbidities related to pulmonary function? Did you measure pulmonary function tests, FEV₁, between the groups, DLCO, etc?

Dr Shen. Yes. In the patient demographics table, we have shown that preoperative lung function was close between the PV and CV groups.

Dr D'Cunha. You said you used CO₂ intraoperatively. When you used CO₂ in the operating room between the groups, this is a technical question, how much CO₂ were you using when you were in the OR and what pressures were you using, and was that comparable between the groups? How did you measure that?

Dr Shen. The pressure is 8 mm Hg in the cases that the etCO₂ is elevated; we will first add the frequency of ventilation. Almost 95% of these patients will have the etCO₂ down when we add the frequency of respiration.

Dr D'Cunha. Let me clarify, did you give CO₂ into the chest as an infusion to help with visualization, though?

Dr Shen. Yes.

Dr D'Cunha. No, okay.

Dr Shen. Yeah.

Dr D'Cunha. The last question is related to your postoperative management in the diagnosis of pneumonia. You mentioned nicely the STS criteria you used for the diagnosis of pneumonia. Can you briefly just tell us how you monitored these patients postoperatively? What was your protocol? Did you get chest X-rays every day on patients, when did you swallow them, etc?

Dr Shen. Could you repeat it again?

Dr D'Cunha. So, in terms of after surgery when you took care of the patients, what's your protocol for monitoring the patients to identify pneumonia? Because if you never look for it, you will not find it. So did you get chest X-ray films every day? Did you just get them as clinically indicated? When do you get your esophagrams postoperatively to identify anastomotic leaks, which may lead to pulmonary complications, etc?

So, what was your protocol or clinical pathway after surgery?

Dr Shen. We did a CXR every day postoperatively to find the possible pulmonary complications after our MIE. In the cases where the patient's temperature was higher than 35%, we will do a white blood count to find the evidence of potential pneumonia.

Dr D'Cunha. Was there any difference in antibiotic use between the groups that could account for a difference in identifying pneumonia after surgery? Did you look at that?

Dr Shen. Actually, we will change our antibiotics if there is evidence of pneumonia.

Dr D'Cunha. Okay. I will stop there. Thank you.

Dr Shen. Thank you.

Dr Wentao Fang (*Shanghai, China*). I have 2 questions for you. First, you mentioned in your study design that you excluded patients with COPD [chronic obstructive pulmonary disease]. To my knowledge, smoking is one of the major causes to the etiology of squamous cell carcinoma in China, and smoking is also one of the main causes for COPD. How could you achieve that?

Dr Shen. Nice comments. A part of the patients who are COPD at our institution received MIE, but I think in the preoperative, COPD may have some effect on our results, so we just excluded it.

Dr Fang. Okay. So, the second one is, I wonder if there was any patient in your study group who could not tolerate the 5-mL tidal

volume during the operation. I mean, those who could not have stable oxygen saturation during the operation?

Dr Shen. First, I think both the PV group and the CV group were stable during their thoracoscopic esophagectomy.

And, the main problem in the PV group was that some patients were experiencing an elevated etCO_2 . And, it is temporary, and I think it is permissive because we just add the frequency of respiratory and it can be overcome in that case.

Dr Fang. I have one comment for you. Actually, instead of lowering the tidal volume, you may switch the pattern of ventilation to pressure control rather than volume control. That would help in COPD patients. Thank you.

Dr Shen. Yes. I think we can try it later. Thank you.